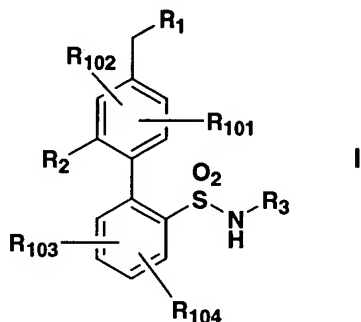
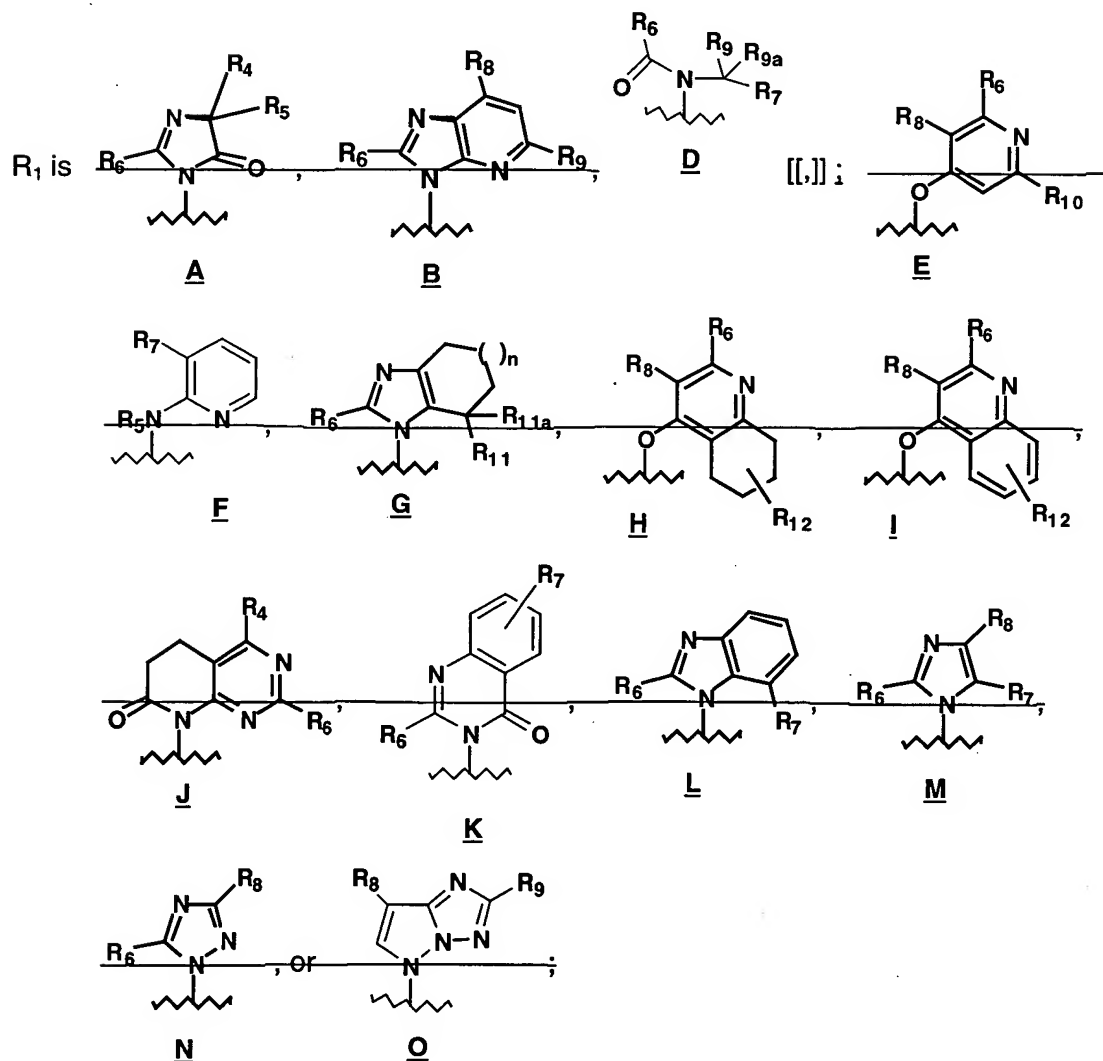


In The Claims:

1. (Currently Amended) A compound of the following formula I, ~~or an enantiomers,~~
diastereomers, salts or metabolite and solvates thereof:



wherein:



R_2 is hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, aryloxy alkoxyalkoxy, cyano, hydroxy, hydroxyalkyl, nitro, -CH(OR₁₃)(OR₁₄), or -(CH₂)_wY; with the proviso that when R_4 is B, R_2 is not hydrogen, halogen, alkyl, haloalkyl, alkoxy, hydroxyalkyl, nitro, -(CH₂)_wNR₁₆R₂₀ or -NHSO₂R₂₂;

R_3 is heteroaryl;

R_4 and R_5 are each independently alkyl, hydroxyalkyl, cycloalkyl, hydroxy substituted cycloalkyl, alkoxyalkyl, or hydroxy substituted alkoxyalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl or tetrahydropyranyl ring which may be optionally substituted with one or more hydroxy groups;

R_6 is alkyl, hydroxyalkyl, haloalkyl, hydroxy substituted haloalkyl, cycloalkyl, hydroxy substituted cycloalkyl, (cycloalkyl)alkyl, hydroxy substituted (cycloalkyl)alkyl, aralkyl, alkoxy, hydroxy substituted alkoxy, alkoxyalkyl, hydroxy substituted alkoxyalkyl, or -NR₁₆R₁₇;

R_7 is -(CH₂)_w-CO₂R₁₅, -(CH₂)_w-(C=O)NR₁₆R₁₇, -(CH₂)_w-NR₁₅(C=O)NR₁₆R₁₇, -(CH₂)_w-CH₂OH, -(CH₂)_w-(C=O)R₁₅, tetrazolyl, oxadiazolyl or triazolyl wherein said tetrazolyl, oxadiazolyl or triazolyl may optionally be substituted with hydrogen, alkyl, hydroxy or halogen;

R_8 , R_9 [1], and R_{9a} , R_{10} and R_{12} are each independently hydrogen, halogen, alkyl, hydroxyalkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, heteroaryl, arylalkyl, alkylthioalkyl, alkoxy or alkoxyalkyl, or R_9 and R_{9a} together with the carbon atom to which they are bonded form a cycloalkyl ring;

R_{11} and R_{11a} are each independently hydrogen, alkoxy, or together form a carbonyl;

R_{13} and R_{14} are alkyl or together form a five to six-membered ring;

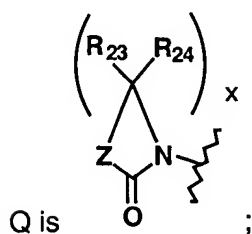
R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl, hydroxyalkyl, cycloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, aralkyl, heterocycloalkyl, aryl, heteroaryl or -(CH₂)_wQ, or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;

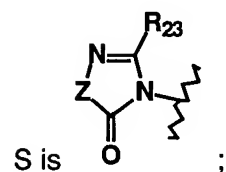
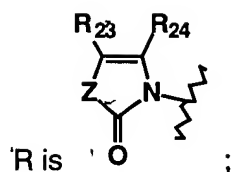
n is 1 or 2;

w is 0, 1, or 2;

Y is heteroaryl, -COOH, -COOR₁₈, -CONR₁₉R₂₀, -NR₁₉R₂₀, -NR₁₉-OR₂₀, -NR₂₁(C=O)R₂₂, -NR₂₁(C=O)NR₁₉R₂₀, -N(R₁₉)-(alk)-NR₂₁(C=O)R₂₂, -NR₂₁(C=O)OR₁₈, -NR₂₁SO₂R₂₂, -SO₂R₂₂,

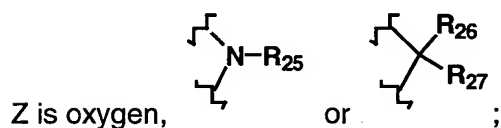
Q, R or S;





R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;



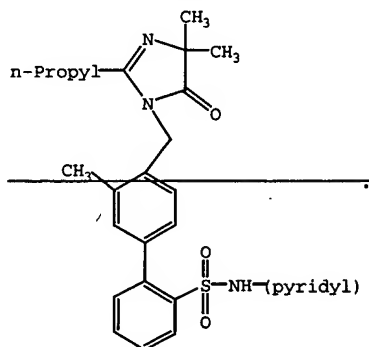
x is 2, 3 or 4;

R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring;

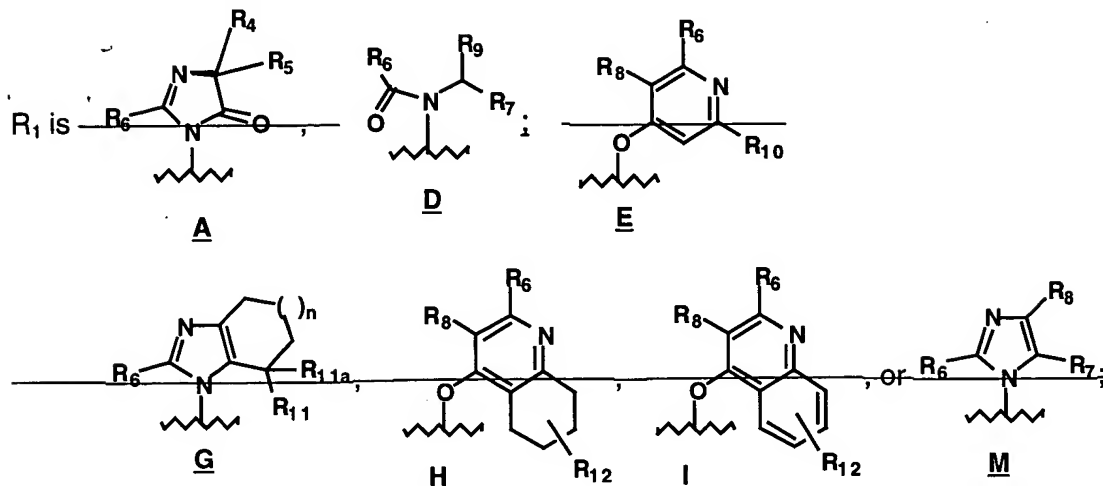
R_{101} , R_{102} , R_{103} , and R_{104} are each independently hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, cyano, hydroxy, hydroxyalkyl, nitro, -CH(OR₁₃)(OR₁₄), or -(CH₂)_wY;

wherein said rings; aryl alone or as part of another group; or heteroaryl alone or as part of another group may each optionally be substituted by one or more hydrogen, halogen, cyano, alkyl, hydroxyalkyl, alkoxy, nitro or trifluoromethyl groups[[:]].

~~provided that when R_4 is \underline{A} said compound is other than~~



2. (Currently Amended) A compound of claim 1, wherein



R_2 is hydrogen, alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY_1$; ~~or when R_4 is D, R_2 is hydrogen, alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY_1$;~~

R_3 is isoxazolyl pyridizynyl, pyrazynyl or pyrimidinyl, each optionally independently substituted with one to three substituents selected from hydrogen, halogen, cyano, alkyl, alkoxy, trifluoromethyl or nitro;

~~R_4 and R_5 are each independently alkyl, cycloalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;~~

R_6 is alkyl, haloalkyl, cycloalkyl or alkoxy;

R_7 is $-CO_2R_{15}$, $-(C=O)NR_{16}R_{17}$ or $-CH_2OH$;

~~R_8 , R_9 , R_{10} and R_{12} are each independently~~ is hydrogen, halogen, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;

~~R_{11} and R_{11a} are each independently hydrogen, alkoxy, or together form a carbonyl;~~

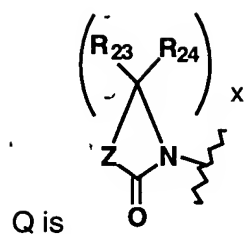
R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl or cycloalkyl or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;

n is 1 or 2;

w is 0, 1, or 2;

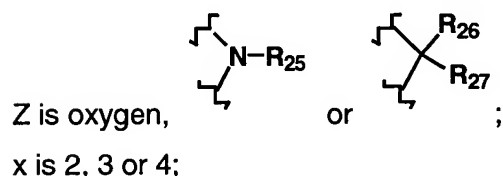
Y is $-COOR_{18}$, $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-NR_{21}(C=O)OR_{18}$,

$-NR_{21}SO_2R_{22}$, $-SO_2R_{22}$ or Q;



R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

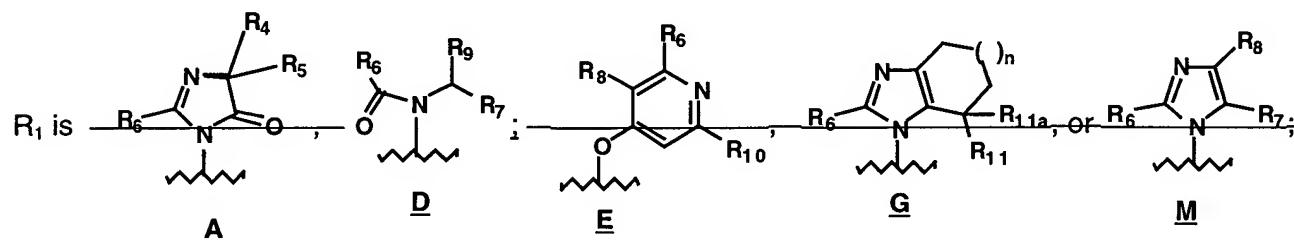
R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;



R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring;

R_{101} , R_{102} , R_{103} , and R_{104} are each independently hydrogen, halogen, alkoxy or alkyl.

3. (Currently Amended) A compound of claim 1, wherein



R_2 is hydrogen, alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, hydroxyalkyl, or $-(CH_2)_wY_i$; or when R_4 is D, R_2 is hydrogen, alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY_i$;

R_3 is isoxazolyl, optionally independently substituted with one or two substituents selected from hydrogen, halogen, cyano, alkyl, alkoxy, trifluoromethyl or nitro;

R_4 and R_6 are each independently alkyl, cycloalkyl, or R_4 and R_6 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;

R_6 is alkyl, haloalkyl, cycloalkyl or alkoxy;

R_7 is $-CO_2R_{15}$ or $-(C=O)NR_{16}R_{17}$;

~~R_8 , R_9 and R_{10} are each independently~~ is hydrogen, halogen, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;

~~R₁₄ and R_{14a} together form a carbonyl;~~

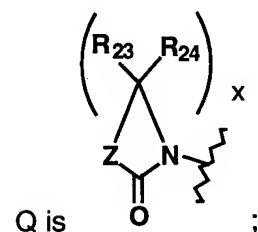
R₁₅, R₁₆ and R₁₇ are independently hydrogen, alkyl, or cycloalkyl or R₁₆ and R₁₇ may together form a four to six-membered heterocyclic ring;

n is 2;

w is 0, 1, or 2;

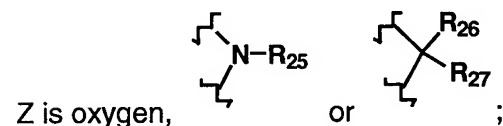
Y is -NR₂₁(C=O)R₂₂, -NR₂₁(C=O)NR₁₉R₂₀, -NR₂₁(C=O)OR₁₈, -NR₂₁SO₂R₂₂,

-SO₂R₂₂ or Q;



R₁₈, R₁₉, R₂₀, R₂₁ and R₂₂ are each independently hydrogen, alkyl, cycloalkyl, or R₁₉ and R₂₀ may together form a four to seven-membered heterocyclic ring;

R₂₃ and R₂₄ are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

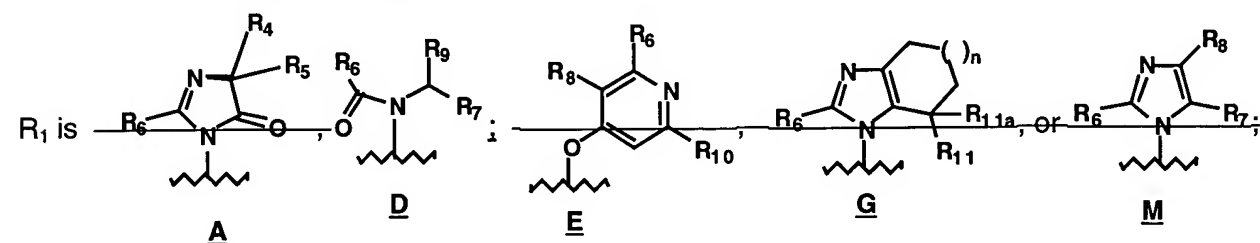


x is 2, 3 or 4;

R₂₅, R₂₆ and R₂₇ are each independently hydrogen, alkyl or cycloalkyl, or R₂₆ and R₂₇ may together form a three to seven-membered cycloalkyl ring;

R₁₀₁, R₁₀₂, R₁₀₃, and R₁₀₄ are each independently hydrogen, halogen, or alkyl.

4. (Currently Amended) A compound of claim 1, wherein



~~R₂ is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or -(CH₂)_wY; or when R₄ is D, R₂ is hydrogen, alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or -(CH₂)_wY;~~

R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen;

~~R_4 and R_5 are each independently alkyl, cycloalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl or cyclohexyl ring;~~

R_6 is alkyl, haloalkyl, cycloalkyl or alkoxy;

R_7 is $-(C=O)NR_{16}R_{17}$;

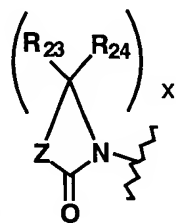
~~R_8 , R_9 , and R_{10} are independently~~ R_8 , R_9 , and R_{10} are independently is H, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;

n is 2;

w is 0, 1, or 2;

Y is $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-NR_{21}(C=O)OR_{18}$, $-NR_{21}SO_2R_{22}$

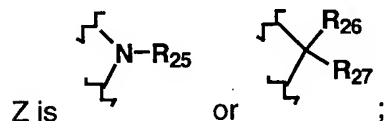
or Q;



Q is ;

R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, cycloalkyl, or R_{19} and R_{20} may together form a four-, five-, six- or to seven-membered heterocyclic ring;

R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;



Z is

or

;

x is 2;

R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three-, four-, five, six- or seven-membered cycloalkyl ring;

R_{101} , R_{102} , R_{103} , and R_{104} are each independently hydrogen, halogen, or alkyl.

5. (Original) A compound of claim 1, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

6-17. (Cancelled)

18. (Currently Amended) A compound of claim 1, wherein R_2 is alkoxyalkyl, ~~alkyl~~, haloalkyl or haloalkoxyalkyl.

19. (Original) A compound of claim 18, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

20. (Original) A compound of claim 1, wherein R_2 is $-\text{CH}_2\text{Y}$.

21. (Original) A compound of claim 20, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

22. (Original) A compound of claim 20, wherein Y is Q.

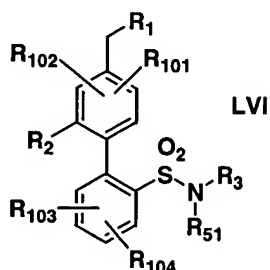
23. (Original) A compound of claim 22, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

24-45. (Cancelled)

46. (Original) A pharmaceutical composition for the treatment of an endothelin-dependent or angiotensin II-dependent disorder, comprising a pharmaceutically acceptable vehicle or diluent and at least one compound of claim 1 in an amount effective therefor.

47-48. (Cancelled)

49. (Currently Amended) A compound of the formula



wherein R_1 , R_2 , R_3 , R_{101} , R_{102} , R_{103} , and R_{104} are as defined in claim 1; and R_{51} is a suitable nitrogen protecting group.

50. (Original) The compound of claim 49, wherein R_{51} is $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{OCH}_3$, or $-\text{CH}_2\text{OCH}_2\text{-aryl}$.

51-60. (Cancelled)

61. (Original) N2-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N2-(1-oxobutyl)-L-valinamide or a salt, enantiomer or diastereomer thereof.

62-68. (Cancelled)

69. (Currently Amended) A compound of claim 68 1, wherein R₂ is hydrogen, alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R₁₀₁, R₁₀₂, R₁₀₃, R₁₀₄ are each independently hydrogen, halogen, or alkyl.

70. (Currently amended) A compound of claim 1 wherein R₂ is -CH₂Y.

71. (Original) A compound of claim 70, wherein Y is Q.

72-92. (Cancelled)

93. (Original) The pharmaceutical composition of claim 46 further comprising at least one ACE inhibitor.

94. (Original) The pharmaceutical composition of claim 93 wherein said ACE inhibitor is selected from captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, or lisinopril.

95. (Original) The pharmaceutical composition of claim 46 further comprising at least one vasopepsidase inhibitor.

96. (Original) The pharmaceutical composition of claim 95 wherein said vasopepsidase inhibitor is selected from omapatrilat or gemopatrilat.

97. (Original) The pharmaceutical composition of claim 46 further comprising at least one HMG CoA reductase inhibitor.

98. (Original) The pharmaceutical composition of claim 97 wherein said HMG CoA reductase inhibitor is selected from pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 or ZD-4522.

99. (Original) The pharmaceutical composition of claim 46 further comprising at least one anti-platelet agent.

100. (Original) The pharmaceutical composition of claim 99 wherein said anti-platelet agent is selected from clopidigrel, ticlopidine, CS-747 or aspirin.

101. (Original) The pharmaceutical composition of claim 46 further comprising at least one anti-diabetic agent.

102. (Original) The pharmaceutical composition of claim 101 wherein said anti-diabetic agent is selected from biguanides or biguanide/glyburide combinations.

103. (Original) The pharmaceutical composition of claim 46 further comprising at least one beta-adrenergic agent.

104. (Original) The pharmaceutical composition of claim 103 wherein said beta-adrenergic agent is selected from carvedilol or metoprolol.

105. (Original) The pharmaceutical composition of claim 46 further comprising at least one mineralocorticoid receptor antagonist.

106. (Original) The pharmaceutical composition of claim 105 wherein said mineralocorticoid receptor antagonist is selected from spironolactone or eplerenone.

107-108. (Cancelled)